Thrombin-mediated activation of Akt signaling contributes to pulmonary vascular remodeling in pulmonary hypertension.

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Public Summary:
Chronic thromboembolic pulmonary hypertension (CTEPH) has been increasingly recognized as a common source of elevated pulmonary vascular resistance and pulmonary hypertension. It is clear that development of pulmonary thromboemboli is the inciting event for this process, yet it remains unclear why some patients have persistent pulmonary artery occlusion leading to distal pulmonary vascular remodeling and CTEPH. Thrombin, a serine protease, is an integral part of the common coagulation cascade, yet thrombin also has direct cellular effects through interaction with the family of PAR membrane receptors. This study is designed to determine the effects of thrombin on Akt signaling in pulmonary artery smooth muscle cells (PASMC) from normal humans and pulmonary hypertension patients. Thrombin treatment of PASMC resulted in a transient increase in Akt phosphorylation and had similar effects on the downstream targets of the Akt/mTOR pathway. Ca(2+) is shown to be required for Akt phosphorylation as well as serum starvation, a distinct effect compared to platelet-derived growth factor. Thrombin treatment was associated with a rise in intracellular [Ca(2+)] and enhanced store-operated calcium entry (SOCE). These effects lead to enhanced proliferation, which is more dramatic in both IPAH and CTEPH PASMC. Enhanced proliferation is also shown to be attenuated by inhibition of Akt/mTOR in CTEPH PASMC. Thrombin has direct effects on PASMC increasing intracellular [Ca(2+)] and PASMC proliferation, an effect attributed to Akt phosphorylation. The current results implicate the effects of thrombin in the pathogenesis of idiopathic pulmonary arterial hypertension (IPAH) and CTEPH, which may potentially be a novel therapeutic target.

Scientific Abstract:
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